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Neuropsycholigical late effects of leukemia treatment in children.

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Summary

The outlook for many patients with acute lymphoblastic leukemia (ALL) has continued to improve but the increasing number of surviving children created the question whether biological cure goes with good quality of life. Chronic side-effects of disease and/or treatment may impede cognitive and psychosocial development and therefore also hinder children from meeting academic demands. In children with ALL, particularly concern has emerged on the iatrogenic effects of central nervous system (CNS) prophylaxis, essential though it was to improve survival. This thesis dealt with the late and persistent neuropsychological sequelae of 3 successive national DCLSG[1] protocols ALL 5, ALL 6 and ALL 7 with different forms of CNS prophylaxis. Accumulating evidence of cognitive decline in children treated on protocol ALL 5 with cranial irradiation (CI) and chemotherapy subsequently sparked investigations on cognitive functioning in children treated with chemotherapy-only (protocols ALL 6 and ALL 7). Patients on any protocol were longitudinally studied by means of repeated neuropsychological assessments (NPA), magnetic resonance imaging (MRI) of the brain and evaluation of school career. We focused on the younger age group (diagnosis < 7 years of age) considering the greater vulnerability of the immature brain for diffuse (radiation induced) damage. Patients in this study were mainly treated at the Children's Cancer Center, University Hospital of Groningen and diagnosed between 1979 and 1992.

The medical background of the patients under study was given in **chapter one.** Incidence, pathogenesis, treatment and outcome of ALL were briefly described. Noteworthy, survival has increased from 50 to 75% from the late-seventies to the mid-nineties (all risk groups combined).

1 Dutch Childhood Leukemia Study Group

Chapter two was a case report. This child, treated on DCLSG protocol ALL 5 at a young age, represented the group of patients who are at risk for the deleterious effects of CI and intrathecal (IT) and intravenous (IV) methotrexate (MTX) on brain functioning. At age 15, this cured girl contended with moderate difficulties in the domains of attention, arithmetic, executive and fine motor functioning besides low-normal intelligence. At age 20, the sequelae of these cognitive deficits had resulted in major vocational problems which clearly and persistently found expression in her first job, 15 years after treatment.

Chapter three summarized an extensive review of the neuropsychological and related literature with special focus on research methodology that may explain the still contradictory results. In pediatric neuropsychology, test shift seems one of the most difficult and almost insurmountable bottlenecks for longitudinal research.
We discussed the possible relationships among risk factors, etiology and specificity of cognitive impairment. There is no doubt that administration of CI (with MTX) is associated with mild to moderate global cognitive deterioration in young children. The plasticity of the immature brain can apparently not sufficiently compensate for diffuse damage acquired at an early age. The relative contribution of chemotherapy penetrating into the CNS is not yet unequivocal. The complex background of this field of research was further illustrated by discussing the neuropathology underlying the occurrence of cognitive decline. Both a necrotizing leuco-encephalopathy and a mineralizing micro-angiopathy have been widely reported in irradiated children but the relationship between neuroradiological and neuropsychological measures remains unclear. We subsequently described the acute and early but transient effects of neurotoxic treatment on mental status. Such effects, like psychological problems, may interfere with optimal cognitive development but must be distinguished from the late and persistent sequelae of leukemia treatment. This chapter ended with placing the ALL

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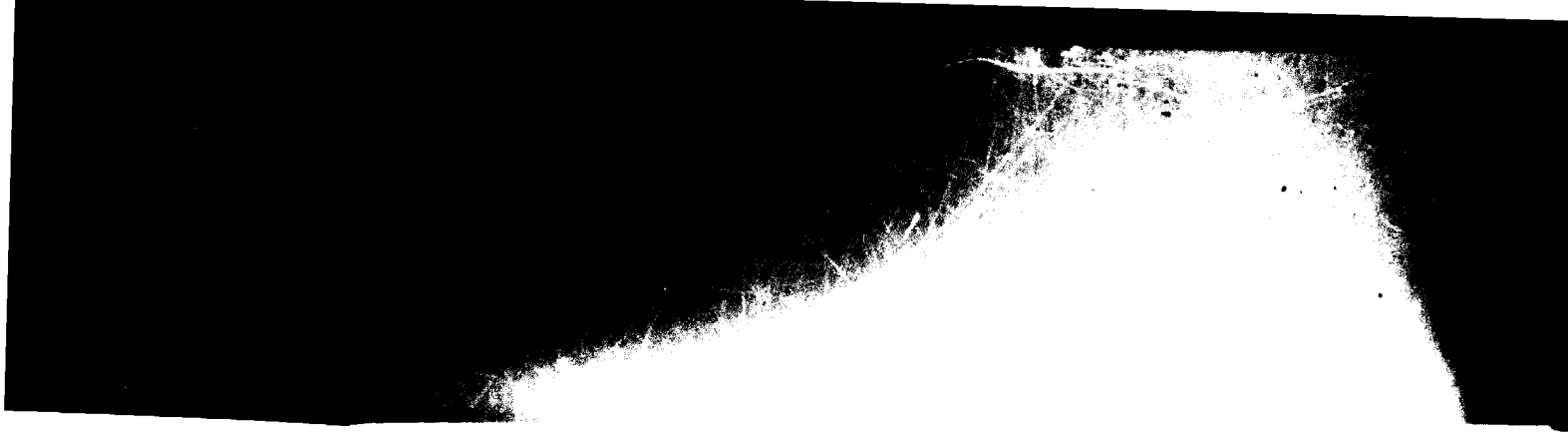
Patients' characteristics, treatment protocols, study design, instruments, hypotheses and statistical analyses were described in **chapter four**.
From 1981 to 1988, 35 consecutive children treated for ALL according the DCLSG protocol ALL 5 or the Groningen High Risk protocol (CI + chemotherapy) were enrolled in this study. They had 2 NPA's after cessation of two years chemotherapy. Median age at diagnosis was 3;5 years, median age at the first NPA was 6;4 years and median age at the second NPA was 11;4 years.
From 1986 to 1990, 17 consecutive patients treated on DCLSG protocol ALL 6 (chemotherapy-only) entered the study. They also has 2 NPA's after completion of 2 years treatment. Median age at diagnosis was 3;5 years, median age at the first NPA was 5;10 years and median age at the second NPA was 9;3 years.
Between 1988 and 1992, 20 consecutive patients treated on DCLSG protocol ALL 7 (also chemotherapy-only) entered a prospective study. A first NPA was performed prior to CNS prophylaxis to obtain a cognitive 'baseline'. Moreover, we wished to investigate the feasibility of examining young children shortly after diagnosis. Then, they had 2 more NPA's after 1½ or 2 years chemotherapy according to the schedule for protocol ALL 5 and ALL 6 patients. Median age of diagnosis and first assessment was 3;6 years, median age at the second evaluation was 5;3 and median age at the last examination was 10;3 years.
Longitudinal participation for the combined study group (n=65) was 92%.

The aim of this series of studies was to evaluate a broad domain of cognitive functioning. Assessments included measures of verbal and performance intelligence, auditory learning and memory, sustained attention and attentional capacity, visual motor integration and fine motor functioning

(yielding 12 psychometric measures in protocol ALL 5 and protocol ALL 6 and 14 measures in protocol ALL 7, at the last assessments). Patients' test performance was compared to healthy peers from the same geographical area. Moreover, protocol ALL 5 patients were compared to children on protocol ALL 6 and the DCLSG protocol ALL 6 group in turn was compared to patients on protocol ALL 7. Additionally, poor performance was determined per test and per each case individually, defined as a standard score at least 1,64 SD below the normative mean for that specific test (representing the lowest 5% of the norm population). Tests with a (predominantly) motor output were distinguished from tests mainly measuring cognition.

An MRI of the brain was scheduled in the year after the second NPA for every patient if aged ≥ 5 years, and compared to psychometric findings. MRI scans were judged normal, probably abnormal or definitely abnormal from 3 types of abnormalities: atrophy, calcifications and signal abnormalities as index for white matter damage. MRI scans could be obtained in 50 cases (89% of the eligible subjects). MRI findings in protocol ALL 5 patients were compared to protocol ALL 6 who were then compared to children treated on protocol ALL 7.

In the late-nineties, school career was evaluated in all patients by questionnaire developed for the neuropsychological research in our institution. Parents reported on possible placements in special primary schools for learning disabled (in Dutch: LOM and MLK schools) and on level of secondary education. These levels were classified through a 6 points scale. Category one was lowest representing special education for children with defective IQ's (in Dutch: VSO-MLK), category four was the mean level for the Netherlands (in Dutch: MAVO) and category six was the highest level preparing for university (in Dutch: VWO). Median follow-up since diagnosis was 13 years for the DCLSG protocol ALL 5 group, near 9 years for DCLSG protocol ALL 6 patients and ample 7 years for subjects treated on DCLSG protocol ALL 7. Patients (n=65 for the combined study group) were



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compared to their healthy siblings (n=98). Participation was 100% in ever study group.
Later, a nationwide study was designed in ALL survivors diagnosed at any age and treated according to DCLSG protocol ALL 5. The school questionnaire was completed by 94 patients and their 134 siblings (participation rate 64%). Median age at evaluation was 20 years and median follow-up since diagnosis was 15 years.

Hypotheses stated lower test scores and school levels in any patient group, compared to healthy controls and siblings, respectively (one tailed testing). Moreover, we expected higher test scores and school levels and less MRI abnormalities for patients treated on protocol ALL 6 with chemotherapy-only compared to irradiated children on protocol ALL 5 (one tailed testing). It was hypothesized that MRI abnormalities would correspond with poorer test performance in any patient group. Younger age at diagnosis and higher CI dose (18 versus 25 Gy in protocol ALL 5 only) were considered risk factors for poorer outcome but female sex was not.
We could study change over time by comparing test results from successive evaluations but we did not specifically expect either improvement or decline (two tailed testing). Only results from the same tests were used for longitudinal comparisons.
Lastly, we were interested in a possible different outcome for either protocol ALL 6 and ALL 7 (both chemotherapy-only) but no specific hypothesis was formulated (two tailed testing). Protocol ALL 6 contained higher cumulative doses of dexamethasone, vincristine and it treatment but on the other hand, protocol ALL 7 was the more intensive treatment.
Emphasis was on the results of the last NPA's, as young age at the first evaluations and test shift would limit the numbers of comparisons for the first assessments. We calculated effect size and 95% confidence intervals. To correct for the high numbers of comparisons, significance levels were

reported at $p \leq 0.004$ (Bonferroni correction). In our articles however, usual levels of $p \leq 0.05$ were also given.
Results were shown in chapters five through nine.

Chapter five described the control group, composed as norm group for new test versions of Rey's auditory verbal learning test (RAVLT). This test is one of the most widely used and relevant word learning and memory tests for children and adults but adequate normative data for Dutch children were still lacking. Moreover, parallel forms were needed to avoid practice effects in a repeated measurements design. We collected normative data for the existing form of the RAVLT and 2 newly constructed parallel forms in a sample of 225 Dutch school children. Except for the use of this study, these test forms have proved very useful in the daily practice of pediatric neuropsychology.

Chapter six offered psychometric test data of the second NPA and MRI findings in 35 children treated at a young age on DCLSG protocol ALL 5 (CI + chemotherapy), including 7 cases with meningeal leukemia. Main purpose of this study was to compare neuroradiological and neuropsychological results, with 8 years follow-up since diagnosis. Results showed that MRI's were classified as definitely abnormal in 51% and as probably abnormal in another 17% of the patients. White matter damage was most frequently seen. MRI abnormalities were not related to sex, CI dose, age at diagnosis and test performance. Patients had significantly lower scores, compared to the norm group on measures of intelligence, short term memory and visual and fine motor functioning. Some lower test scores significantly correlated with younger age (diagnosis < 4 years versus > 4 years) or higher CI dose (25 - 32 Gy compared to 18 - 20 Gy) but not with meningeal leukemia as such. Forty percent of the patients had to be referred to schools for learning disabled. We concluded that ALL treatment including CI and chemotherapy at a young age was associated with persistent cognitive impairment and (non-related) MRI abnormalities.

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In **Chapter seven** school career was evaluated in 94 long term survivors, treated with CI and chemotherapy according to DCLSG protocol ALL 5 at any age in comparison to their 134 siblings (a nationwide study).
Results showed that significantly more patients than siblings (n = 12 versus n = 1) were placed in special primary schools. Mean level of secondary education in the patients was also significantly lower than in siblings (level 3.4 versus 4.5 respectively; 4 was the mean level for the Netherlands). But, the majority of patients was not mentally retarded and it was questioned whether the 1.1 point difference is clinically important. No effect of gender or CI dose (25 Gy versus 18 Gy) was found. In contrast, younger age at diagnosis was strongly related to both more referrals to special primary education and lower final educational level. Only in patients diagnosed at an age ≥ 7 years, no significant differences were found in comparison to siblings. We concluded that treatment for childhood ALL at a young age with either 18 or 25 Gy CI and chemotherapy was clearly associated with poorer academic career.

Chapter eight, offered all results in 17 subjects treated at a young age according to DCLSG protocol ALL 6 with chemotherapy-only. At the last NPA (median follow-up 5 years after diagnosis), patients performed significantly worse than controls on measures of auditory memory and fine motor functioning. Considering individual cases, 17 patients combined performed poorly on 16 measures, 9 motor scores included. Seven cases had at least one below-average score on a cognitive test but only one child had a low (verbal) IQ. MRI scans could be obtained in 16 subjects; probably abnormal scans were found in three and definitely abnormal scans in another three children (combined 38% abnormality), but abnormalities did not correlate with lower test scores. Seventeen patients and their 33 siblings did not significantly differ in school placements and levels. These nonirradiated protocol ALL 6 patients demonstrated significantly higher verbal IQ's, better attentional capacity, less learning disability and less MRI abnormalities than

28 ALL 5 patients (excluding 7 cases with meningeal leukemia). On an individual level, 28 subjects on protocol ALL 5 performed poorly on 56 measures, 25 motor scores included. Eleven children had at least one below-average score on a cognitive test and 5 subjects had a low verbal or performance IQ. We concluded: (1) treatment on protocol ALL 6 may be associated with some cognitive impairment compared to controls but fortunately these children reach school levels equal to their siblings so far; 2) protocol ALL 6 patients demonstrated better cognitive functioning and less MRI abnormalities than the irradiated children on protocol ALL 5.

In **chapter nine** we reported all results for 20 children treated at a young age on DCLSG protocol ALL 7 with chemotherapy-only. We found no developmental delay at the start of therapy in a subset of 14 patients who were old enough to complete the Wechsler Intelligence test and Beery test of visual motor integration. Moreover, it proved feasible to perform such examinations shortly after diagnosis. At the last NPA (median follow-up 7 years since diagnosis) significantly lower scores for patients in comparison to controls were found for one attention measure only. Considering individual cases, 20 patients combined performed poorly on 24 measures, 5 motor scores included. Ten children had at least 1 below-average score on a cognitive test and 2 subjects had an low verbal or performance IQ. MRI scans could be obtained in 10 subjects; one MRI was unevaluable, probably abnormal scans were found in two cases but no definitely abnormal scans were found (combined 22% abnormality). No great differences were seen between school achievement in 20 patients and their 17 siblings. We concluded that (1) children treated on protocol ALL 7 had no major cognitive impairment and (2) the slightly better outcome for ALL 7 patients in comparison to protocol ALL 6 (on memory and attention tasks) may indicate possible adverse effects of more dexamethasone and it treatment in the latter. The addendum of chapter 9 offered the comparisons of MRI results for ALL 7 and ALL 6 patients.

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Chapter ten offered a general discussion and conclusions. First, we described the ideal prospective-longitudinal study on neuropsychological sequelae in children treated for leukemia. Unfortunately, young age for the majority of ALL patients leads to major conceptual and methodological bottlenecks. It was a challenge to design and initiate a multicenter prospective study in newly diagnosed patients aged 4 to 12 treated on the current DCLSG protocol ALL 9. This study, including sibling controls and applying a comprehensive test battery started in 1998 and will continue until 4 years follow-up is reached. In this ongoing study, special attention will be paid to attentional and memory skills as most sensitive test measures in the previous series of studies. Next, we discussed the limitations and strengths of our research. Small numbers reduced the power to detect possible differences, if any, between patient groups and controls and among subgroups of patients at risk. Strengths included a standardized longitudinal design and high participation rates of representative study groups. Subsequently, we returned to our hypotheses. It was confirmed that irradiated patients (protocol ALL 5) suffered more cognitive impairment than controls and nonirradiated children. In contrast, it was **not** confirmed that children treated with chemotherapy-only would still show significantly poorer performance across the whole test battery than controls.

Slight differences between both chemotherapy groups (ALL protocol 6 and 7) tentatively supported evidence that corticosteroids may affect cognitive functioning.

According to our hypothesis, lower age at diagnosis was associated with poorer test performance in irradiated children only. Many other studies also revealed a clear age effect with cognitive disabilities more apparent in children irradiated with 18 - 25 Gy below the age of 5 to 7 years which is congruent with the susceptibility of the immature brain to systemic pathological influences. As expected, MRI abnormalities (white matter damage, atrophy and calcifications) were most often found in irradiated

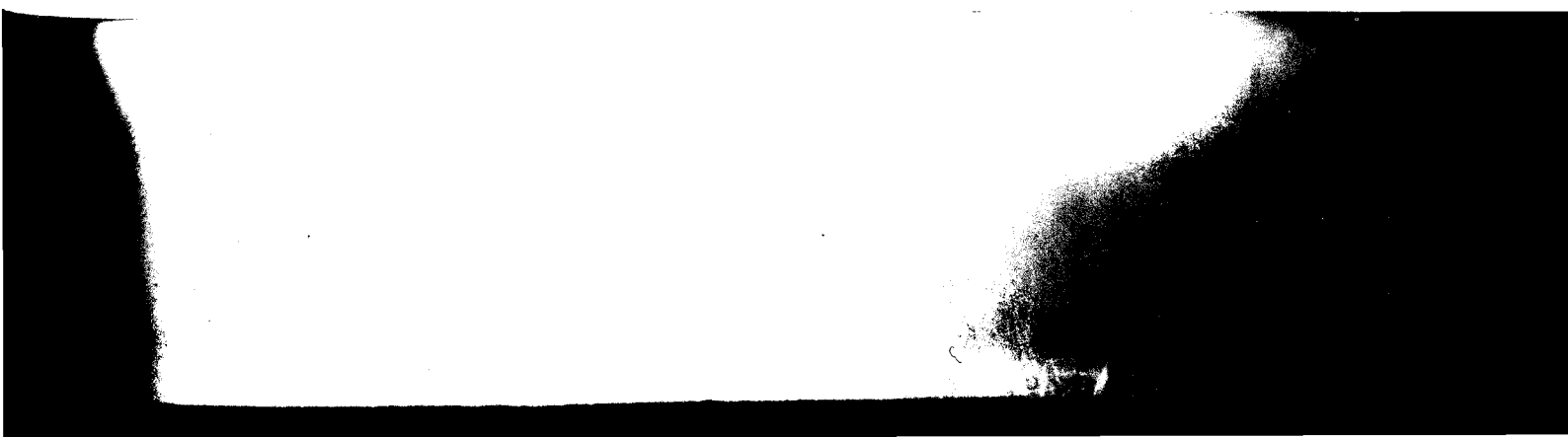
children. We have tried to relate cognition to anatomy in order to identify the structural damage underlying the neuropsychological deficits in ALL survivors. However, test results and school achievements were not related to MRI findings, rejecting our hypothesis. To counsel individual patients who experience deficits in school or vocational life, neuropsychological assessments seem more essential than MRI examinations.

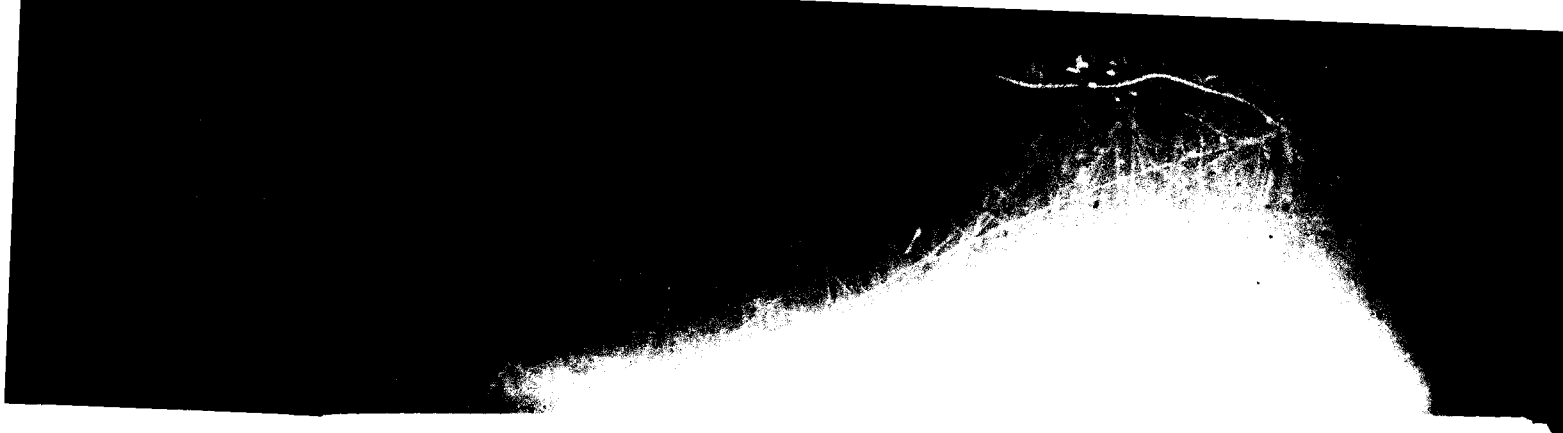
Contrary to some other studies, we did not find an additional adverse effect of female gender in any study group. Another risk factor, which could not be tested as such, emerged from clinical experience: Pre-existing psychopathology seemed to invigorate cognitive disabilities, if present. We therefore need to offer prompt additional support to such children who manifest with mental or behavioral disturbances.

Test performance remained mostly stable after cessation of chemotherapy in all study groups with no significantly decline as suggested by other investigators. However, we don't know yet what may happen to brains after exposure to irradiation or chemotherapy in the very long term. So far, children treated on chemotherapy protocol ALL 6 and protocol 7 have reached normal levels of secondary education but slight memory or attention disturbances may result in vocational handicaps much later in life.

The discussion was closed with a look into the future of the child treated for leukemia. Our results may be reassuring for patients who did not receive CI but we still need to develop intervention programs for the few individuals who do experience cognitive disability. Results of individual assessments have already been employed to implement remedial teaching programs. Psychologists must participate in late effects clinics to evaluate eventual job success or failure, among other things.

Thus, neuropsychology in pediatric oncology centers must serve several goals: (1) individual (neuro)psychological assessment for those patients who experience difficulties or mental deficits which may be related to disease and treatment; (2) intervention and counseling based on such individual diagnostic procedures; (3) continued availability in late effects clinics with





the purpose of timely detection of possible cognitive deterioration in the long term and (4) evaluation of the neurotoxicity of treatment by which neuropsychology can contribute to the development of new protocols yielding best survival with optimal quality of life.